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Mucormycosis in COVID Patients: A Clinico Epidemiological Investigation

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ABSTRACT

Mucormycosis is caused by fungi from the order Mucorales. Humans become infected primarily through sporangiospore inhalation but also through contaminated food or traumatic inoculation. In the context of COVID-19 expression, there has been a significant increase in the prevalence of invasive fungal infection (IFI), specifically Mucormycosis and Aspergillosis. The purpose of this prospective study was to determine the role or relationship of many known and many speculated factors in the occurrence of this disease. This was an observational study to assess the many factors that contributed to an unexpected increase in mucormycosis during the COVID-19 pandemic in India. The current study was conducted at a tertiary level postgraduate institute in India. Demographic information, clinical and analytical data were collected. There was multidisciplinary treatment, including antifungals and surgical treatments. This study comprised 98 mucormycosis patients who were diagnosed based on clinical and radiological symptoms and later validated by microbiological studies. Out of 200 individuals, 120 (60%) were post COVID, 6 (3%) were antigen negative for COVID and 74 (37%) had no history of COVID. Sixty-six percent of 120 post-COVID participants were known diabetics, 15.83% were newly diagnosed, and 27.5% were nondiabetic. 34 (45.94%) of the 74 patients with no history of COVID were known diabetics, 22 (29.72%) were newly diagnosed and 18 (24.32%) were non-diabetic. Mucormycosis is a potentially fatal condition with a significant death rate in India. Diabetes mellitus was identified as the key predisposing factor in the current investigation, which must be taken into consideration for a better understanding of the condition and to lessen its severity.

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Key Words
Aspergillosis, COVID-19, Mucormycosis, Sporangiospores

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INTRODUCTION

The Covid-19 symptom spectrum spanned from common clinical symptoms such as fever, cough, lethargy, myalgia and pneumonia to involvement of many organ systems. It has been linked to an increase in the occurrence of secondary bacterial and fungal infections[1]. Fungal co-infections related with COVID-19 were detected last year as well but they grew rapidly during the second wave. Mucormycosis is a rare but deadly illness that complicates the course of severe COVID-19[2]. Mucormycosis, a rare and potentially fatal fungal infection, has seen an unprecedented rise in the middle of the worldwide Coronavirus disease 2019 (COVID-19) pandemic. India, which has a large SARS-CoV-2 infected population, had the highest number of cases of mucormycosis, particularly during the second wave of COVID-19[3,4]. Interestingly, even before the pandemic, the Indian subcontinent had more mucormycosis patients than the rest of the world. The country's high diabetic population explains this variation[5]. This sudden increase in the number of COVID19-associated mucormycosis (CAM) cases has been explained by a combination of hyperglycemic state induced by the SARS-CoV-2 as well as drugs used during its therapy (especially steroids), hypoxic conditions in affected patients, severe acidosis, higher levels of iron in the form of raised ferritin levels and other factors supporting the host's immunosuppressed condition[6-8].

Early detection of Mucormycosis is critical since it can enhance result. According to studies, it improves survival and may also lessen the necessity for or extent of surgical resection, deformity and pain[9,10]. Both antifungal and surgical management are recognised as the treatment's backbones, nonetheless, both face difficult challenges, such as medication toxicity and anatomic location of lesions[11]. All COVID-19 patients must be regularly watched for immunosuppression squeals. The existence of risk factors increases the burden of care for COVID-19 patients. Mucormycosis is primarily associated with immunocompromised patients the most common comorbidity was diabetes, but COVID in India provided the necessary ingredient, because India has a higher incidence of mucor the combination of COVID and diabetes resulted in an abrupt increase in mucor in the country[12,13].

The goal of this study was to determine the relationship between COVID and many other characteristics such as uncontrolled diabetes the use of more than desired clinical dose of antibiotics and steroids and other immunecompromised condition. This study included a significant amount of COVID.

MATERIALS AND METHODS

This was an observational research to assess the many factors that contributed to an unexpected increase in mucormycosis during the COVID-19 epidemic in India. The current study was conducted at a tertiary level postgraduate institute in India, where a separate multidisciplinary team was formed to treat this condition. After obtaining informed consent from the patients/attendants, we included in our analysis all adult patients presenting with clinical history, symptoms, and signs suggestive of mucor with radiologically and/or microbiologically confirmed cases admitted to clinical departments of the current study hospital. After obtaining informed consent from the patients/attendants, we included in our analysis all adult patients presenting with clinical history, symptoms, and signs suggestive of mucor with radiologically and/or microbiologically confirmed cases admitted to clinical departments of Tertiary care teaching hospitals.

Adults with symptoms and signs of facial swelling (unilateral/bilateral), headache, fever, a black lesion on the face, nasal bridge, or within the mouth that quickly worsens, sinus congestion, shortness of breath, cough, abdominal discomfort, delirium, or coma were considered. Nasal endoscopy findings, KOH stain, histopathology findings, and radiographic examinations all confirmed clinical cases.

Mucormycosis was diagnosed based on clinical findings, KOH stain and histopathological findings of ribbon-like and broad-based hyphae with wide-angle branching and radiographic examinations. COVID-19 was confirmed in patients using RT-PCR or a rapid antigen test (RAT) from nasopharynx tissues. Individuals who presented with mucormycosis without a history of COVID were also included in our study.

We collected the following information using a standardised proforma demographic data, COVID-19 history, severity, length of symptoms, different locations of mucor involvement, hospitalisation (ICU/ward stay), or suggested home isolation history during COVID. We looked into the therapeutic options available to patients. We inquired about the usage of antibiotics, glucocorticoids, antiviral medicines, biologicals and other COVID alternative treatments. Participants were quizzed on the use of oxygen masks, canulas, cylinders and humidifiers. A comorbidity history was sought. Nasal swab KOH mount, CD4 cell count, HIV antibody test, COVID antibody test in individuals who had no history of COVID-19 and were COVID antigen negative, HbA1c, diagnostic nasal endoscopy (DNE) and biopsy, radiological investigations and mortality outcome were all investigated. All of this data was recorded and analysed.

Statistical analysis: The collected data was assembled and input into a spreadsheet programme (Microsoft Excel 2007) before being exported to the data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). The confidence level and level of significance for all tests were set at 95-5%, respectively.

RESULTS

One patient was less than 20 years old, 12 (6%) were 21-30 years old, 40 (20%) were 31-40 years old, 72 (36%) were 41-50 years old, 36 (18%) were 51-60 years old, and 39 (19.5%) were older than 60 years old. Table 1 shows that 156 (78%) were male and 44 (22% were female).

Out of 200 individuals, 120 (60%) were post COVID, 6 (3%) were antigen negative for COVID and 74 (37%) had no history of COVID. 12 (6%) were vaccinated, whereas 188 (94%) were not. 52 (26%) patients had a duration of less than 10 days between COVID and mucormycosis, 36 (18%) patients had a duration of 10-20 days between COVID and mucor, 38 (19%) patients had a duration of more than 20 days between COVID and mucormycosis, and 68 (34%) patients did not have a history of COVID-19. (Table 2) Out of 200 admissions, 70 (35%) had less than or equal to seven days of glucocorticoid usage during COVID, 40 (20%) had more than seven days of use and 90 (45%) had no history of steroid use. Out of the 200 patients, 180 (90%) had no history of mask reuse, while the remaining 20 (10%) did (Table 3).

Sixty-six percent of 120 post-COVID participants were known diabetics, 15.83% were newly diagnosed, and 27.5% were nondiabetic. 34 (45.94%) of the 74 patients with no history of COVID were known diabetics, 22 (29.72%) were newly diagnosed and 18 (24.32%) were non-diabetic. There were six COVID-negative patients, three (50%) of whom had previously been identified as diabetes, two (33.33%) were newly diagnosed and one (16.66%) was not diabetic (Table 4).

There were 54 RM, 42 ROM, and 24 ROCM among the 120 post-COVID subjects.

Table 1: Age and gender distribution of study participants

Age (years)	No of patients	Percentage
<20	1	0.5
21-30	12	6
31-40	40	20
41-50	72	36
51-60	36	18
>60	39	19.5
Gender		
Male	156	78
Female	44	22

Table 2: History of COVID status and duration between COVID

COVID status	No of patients	Percentage
Post COVID	120	60
COVID negtive	6	3
No history of COVID	74	37
Total	200	100
Duration in days		
COVID negtive	6	3
<10 days	52	26
	36	18
	38	19
10-20 days	68	34
>20 days	200	100

DISCUSSIONS

Covid 19 is linked to immunological dysregulation produced by the SARS-CoV-2 virus. It causes an increase in inflammatory cytokines and reduced cell-mediated immunity, with lower cluster of differentiation (CD4+ T and CD8+ T) cell numbers, making them more susceptible to fungal co-infections.14 White et al and Song et al found a rise in the incidence of invasive fungal illness in patients with covid 19[15,16].

Although Mucormycosis is relatively rare in healthy people, it is predisposed to by a number of immunocompromised diseases. Uncontrolled diabetes with or without DKA, haematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxamine or desferrioxamine therapy, voriconazole prophylaxis for transplant recipients, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma are all included[8].

Mucormycosis became more common in India beginning in May 2021. We attribute this rise primarily to the COVID-19 pandemic (second wave). The majority of cases had a time interval of fewer than 10 days between COVID and mucormycosis. This outbreak was mostly caused by improper glucocorticoid and antibiotic doses. Glucocorticoids and antibiotics were utilised in greater quantities than the desired clinical dose during the COVID pandemic (second wave).

As in earlier investigations, 156 (78%) of the patients with mucormycosis in our study were men[8-18]. Diabetes was identified as a major underlying comorbidity in both COVID-associated mucor and persons without a history of COVID. SARS-CoV-2 primarily damages pancreatic insulin-producing cells (B-cells), resulting in diabetes[19,20]. The COVID antibody test was positive in those who had no history of COVID and had negative COVID antigens but had COVID signs and symptoms. HbA1c values were also assessed in all diabetic participants, indicating that a large number of people had uncontrolled diabetes. The majorities (56.6%) of 120 post-COVID patients were known diabetics, 15.83% were newly diagnosed and 27.5% were non-diabetic. 45.94% of the 74 individuals with no history of COVID were known to be diabetic, 29.72% were newly diagnosed and 24.32% were non-diabetic. Of the six COVID-negative patients, half were diabetic, 33.3% were recently diagnosed and 16.6% were not.

Mucor is a saprophytic fungus that is found throughout nature, particularly in soil, air, decaying

Table 3: History of steroid use and use of alternative medicine among study participants

Use	Duration	No patients
Yes	<7	70 (35)
	>7	40 (20)
No		90 (45)
Total		200 (100)
Alternative medicine used		
Used		**Number of patients**
Yes		15 (7.5)
No		185 (92.5)
Total		200 (100)

Table 4: Clinical examination including diabetes status among study participants

Variable	No of post-COVID patients (%)	No of COVID-9 negtive patients (%)	No of patients withno history of COVID-19 (%)
Known diabetic	68 (56.6)	3 (50)	34 (45.94)
Newly diagnosed diabetic	19 (15.83)	2 (33.3)	22 (29.72)
Non-diabetic	33 (27.5)	1 (16.66)	18 (24.32)
Total	120	6	74

vegetation and organic materials. It may be present as a commensal in the nasal mucosa. It can infiltrate the paranasal sinuses, orbit and brain when there is a breach or an immunocompromised state. Mucormycosis refers to fungal infections produced by the order Mucorales. Rhizopus spp., Mucor spp. And Lichtheimiaspp. are the most commonly reported pathogens in mucormycosis[21]. Hyperglycemia increases endothelial receptor GRP78 expression, leading in polymorphonuclear dysfunction, poor chemotaxis and faulty phagocytosis[22]. Hyperglycemia and ketoacidosis promote the germination and proliferation of fungal spores found in the environment. Corticosteroids used in COVID 19 by causing impaired neutrophil function and hyperglycemia make diabetic patient more vulnerable for development of mucormycosis[23].

Our study suggests advanced age as a major factor related to hospitalization, respiratory system failure, admissions in ICU and glucocorticoid use in COVID[24,25]. Being older than 50 years was major factor related to mortality in our institute. Bala *et al*.[24] found that Thirty-four (83%) of the patients in their study were males. Out of which 71% were reported from India. In a study conducted by Roden *et al*.[26] of 929 patients diagnosed with Mucormycosis the mean age was 38.8 years, and disease was more common in males (65%) as compared to females (35%). In the study conducted by Manesh *et al*.[27] the mean age was 40.43 years and the most common in males (72%) as compared to females. We did not observe many cases of pulmonary and gastrointestinal mucor. As there are minimum cases showing involvement of respiratory and gastrointestinal systems, we think it could be due to the complications of COVID or treatment related to COVID, rather than a sole modification in the respiratory or gastrointestinal systems. Several pulmonary or gastrointestinal mucor cases have not been diagnosed because it is difficult to obtain respiratory or gastric samples in critical patients admitted to ICU.

The treatment involves antifungal therapy to be started as soon as possible and surgery of the infected part, where feasible. The major drawbacks in the treatment of mucor were the financial conditions of the individuals and the gap in treatment protocol. They could not afford costly antifungals Posaconazole was mainly used when we did not see a favorable response after giving Amp-B[28]. An analysis from South India of the safety and efficacy assessment of posaconazole in an ROCM study showed no mortality, around 66.6% were completely cured, and the rest of the individuals showed improvement in their condition[29]. The new antifungal isavuconazole has shown similar effectiveness to Amp-B. It is recent to the Indian market and its effectiveness still requires assessment[30].

Timely and appropriate dosing of antifungals and surgery, where feasible, are essential in the treatment of mucor. The optimal dose and duration of antifungals are not clear in mucormycosis management. An RCT could be done to assess the results of combining antifungals in mucormycosis management. Around 7% of mucormycosis patients were managed with alternative medicine during their COVID infection.

Present study aims to understand the clinicoepidemiological profile of the patients who were suspected to be of Mucormycosis. The limitation of the study is though it is an epidemiological study the exact incidence or prevalence of Mucormycosis was difficult to assess in different risk groups. Though the predisposing factors were assessed but the strength of association could not be described as there is no control group. The study results may not be generalizable where haematological malignancy and transplantation are the dominant risk factors.

CONCLUSION

Mucormycosis is a potentially fatal disease with a high fatality rate in India. Diabetes mellitus was identified as

the key predisposing factor in the current investigation, which must be taken into consideration for a better understanding of the condition and to lessen its severity. Multidisciplinary collaboration and prompt therapies such as antifungal medication, strict glycemic control and surgical debridement can help minimize mortality. Mucormycosis is universally associated with low iron levels, although the effect of zinc needs to be investigated further.

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